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Pattern of Ascending Aortic Dimensions Predicts the Growth Rate of the Aorta in Patients With Bicuspid Aortic Valve

Alessandro Della Corte, MD, PhD,* Ciro Bancone, MD, PhD,* Marianna Buonocore, MD,* Giovanni Dialetto, MD,* Franco E. Covino, MD,* Sabrina Manduca, MD,* Giancarlo Scognamiglio, MD,† Veronica D'Oria, MD,* Marisa De Feo, MD, PhD*

Naples, Italy

OBJECTIVES This study sought to identify risk factors for rapid growth of the ascending aorta in patients with bicuspid aortic valve (BAV) disease, taking into account its phenotypic variability.

BACKGROUND Phenotypic heterogeneity of BAV-related aortopathy has recently been widely recognized. However, few studies have addressed the determinants of aortic growth so far, not distinguishing among morphological phenotypes.

METHODS Serial retrospective data on 133 adult outpatients with BAV undergoing echocardiographic follow-up were analyzed to search for factors associated with aortic diameter growth over time and with rapid aortic growth (fifth quintile of growth rate distribution), focusing on the impact of different valve morphotypes (i.e., cusp fusion pattern: right-left coronary [RL] and right-noncoronary [RN]) and previously defined aortic phenotypes (nondilated aorta, ascending dilation, root dilation).

RESULTS The RL pattern was present in 69% of patients with BAV and RN in 31%. At baseline, an ascending dilation phenotype was observed in 57% of patients and a root phenotype in 13.5%. No patient with RN-BAV had a root dilation phenotype at either baseline or last examination. Follow-up time averaged 4.0 $\pm$ 2.7 years (535 patient-years). The mean growth rate was 0.3 mm/year at the sinuses and 0.6 mm/year at the ascending level. Aortic regurgitation predicted an increase in ascending diameter over time (odds ratio [OR]: 2.3; $p = 0.03$). Root phenotype at presentation, not absolute baseline diameter, was an independent predictor of fast progression (>0.9 mm/year) for the ascending tract (OR: 14; $p = 0.001$). Fast growth was rarely seen in patients with the RL morphotype and ascending phenotype (6% at the root and 10% at the ascending level).

CONCLUSIONS In patients with BAV, the root phenotype (aortic dilation predominantly at the sinuses, with normal or less dilated ascending tract) may be a marker of more severe aortopathy, warranting closer surveillance and earlier treatment. The more common ascending phenotype proved to be a more stable disease entity, generally with slower progression. (J Am Coll Cardiol Img 2013;6:1301–10)

From the *Cardiac Surgery Unit and Echocardiography Service, Department of Cardiothoracic Sciences, Second University of Naples, V. Monaldi Hospital, Naples, Italy; and the †Cardiology Unit, Department of Cardiothoracic Sciences, Second University of Naples, V. Monaldi Hospital, Naples, Italy. Funded by a "Ricerca Finalizzata" grant (GR09-1580434) from the Italian Ministry of Health. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Although first pointed out as early as 1999 (1), the heterogeneity of bicuspid aortic valve (BAV) in terms of aortopathy risk and features remain often disregarded, both in research and clinical guidelines (2,3). The natural course of bicuspid aortopathy can vary, ranging from indolent aortic diameter growth to rapid progression or earlier occurrence of life-threatening aortic complications (4,5). So far, no established risk marker is available to help define the prognosis of aortopathy in individual patients with BAV, especially in terms of expected rapidity of aortic growth.

Two sources of BAV disease heterogeneity are the morphology of the aortic valve and the shape of the aorta. Valve morphology has been classified by Sievers and Schmidtke (6) according to the number of cusps and the pattern of congenital cusp fusion. The 2 most frequent morphotypes are believed to have distinct underlying developmental defects and to potentially imply different risks and features of aortopathy (7). There is no consensus classification of the shapes that a dilated or aneurysmal ascending aorta can assume; the use of different criteria and imaging methods has led to diverging nomenclature (8–10). In 2006, based on the analysis of 552 patients with aortic dilation, we suggested the distinction between a "root type" of dilation (i.e., with sinuses of Valsalva enlarged to a greater extent than the tubular portion) and an "ascending type" (i.e., dilation predominantly located distal to the sinotubular junction [STJ]) (11). Subsequently, the distinction between root phenotype and ascending phenotype has been adopted in several studies on BAV (8,12,13). Of note, the smooth muscle cells in the sinus portion embryologically derive in part from the secondary heart field, whereas those in the tubular tract originate from the neural crest (14).

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

BAV = bicuspid aortic valve

MVP = mitral valve prolapse

RL = right-left coronary

RN = right-noncoronary

STJ = sinotubular junction

The aim of the present retrospective longitudinal study was to assess the determinants of bicuspid aorta growth rates over time, focusing on the possible impact of valve morphotypes and aortic phenotypes on the progression of the aortopathy.

METHODS

Patient cohort. Our echocardiography database was reviewed to select serial examinations performed in outpatients with isolated BAV. Forty-eight percent of patients were first referred for symptoms, 24% for radiological evidence of increased aortic diameter, 22% were known to have a "congenital murmur," and none had been previously followed up systematically. We also included patients with undefined valve morphology at pre-operative serial echocardiography (usually for severely calcific stenosis) but who later received intraoperative inspective and pathology diagnosis of congenital BAV. Exclusion criteria were unicuspid aortic valve, associated significant congenital or acquired cardiac diseases (e.g., moderate or worse dysfunction of another valve, endocarditis, coarctation), systemic syndromes (e.g., Marfan, Loeys-Dietz, Ehler-Danlos, Turner), and previous cardiac surgery. From a total of 726 echocardiograms recorded between January 2000 and May 2011 in 150 outpatients with BAV who fulfilled the inclusion/exclusion criteria, 716 were serial examinations in 143 patients with at least 1 year of follow-up. Three patients were then excluded because of left-coronary to noncoronary leaflet fusion (the rare left-noncoronary morphotype); another 7 were excluded because of pediatric age at presentation. The definitive study group included 133 patients (age range 18 to 77 years). The study conformed to the Declaration of Helsinki and received local institutional review board approval.

Variables. Three experienced operators performed all echocardiographic examinations. Aortic stenosis severity was graded by integration of Doppler methods, continuity equation, and planimetry; aortic regurgitation (AR) degree was defined by composite evaluation of proximal jet width, abdominal aortic Doppler imaging, and left ventricular end-diastolic dimension (15,16). Bicuspidy of the aortic valve was defined by a systolic fish-mouth appearance of the orifice in parasternal short-axis views (1). Valve morphotype (i.e., the pattern of cusp fusion) was categorized as right-left coronary (RL) (fusion between right and left coronary cusps) or right-noncoronary (RN) (between right and noncoronary cusps) (6). Initially doubtful definitions of the morphotype (37 patients) were resolved by collegial re-review, cardiac magnetic resonance, or 3-dimensional echocardiography.

The aorta was measured twice (inner-edge to inner-edge method) by bidimensional imaging in parasternal long-axis views at the root (maximal dilation of the sinuses of Valsalva), STJ, and ascending aorta (at its maximal diameter). The tubular tract was routinely visualized as much distally (at least 2 to 3 cm) to the STJ as possible. A random sample of 55 examinations was repeated by a blinded operator, showing good reproducibility (Spearman's r between 0.88 and 1.0 and Bland-Altman p values >0.05). For each patient, the expected normal aortic diameters were calculated using the Roman formulas (17). The aorta was defined as dilated if the aortic ratio exceeded 1.15 cm, corresponding on average to >3.8 cm, 2 SD above the mean expected diameter in the present study population at baseline (8,18). Given the mean body surface area (BSA) of 1.8 m^2, this definition of aortic dilation corresponded to a mean size index of ≥2.1 cm/m^2 (5,17). The pattern of aortic dimensions was categorized in 3 aortic phenotypes: no-dilation phenotype, ascending phenotype (dilated ascending aorta with normal or less dilated root), and root phenotype (dilated root with normal or less dilated ascending aorta) (8). Irrespective of the ascending dimension, a small root, defined as aortic ratio <0.9, corresponding on average to <2.9 cm, defined an aortic root smaller than normal (8).

Other variables considered included hypertension, atherosclerotic disease, chronic obstructive pulmonary disease (COPD), mitral valve prolapse (MVP), left ventricular ejection fraction, left ventricular end-diastolic diameter, stroke volume, and interventricular septal thickness (8). Possible presence of AR (at least moderate) plus MVP, a previously reported peculiar association (19), was also recorded. Any increase in the degree of aortic stenosis or regurgitation during follow-up was recorded as well.

Outcome measures. Aortic growth rate was defined as the difference between the diameter at last control and the diameter at presentation, divided by the follow-up time interval in years. A progressing aortic diameter was defined as any positive growth rate (>0 mm/year). A fast progression was defined as a growth rate falling within the fifth quintile of distribution of the growth rate variable. "Phenotype changes" were defined as changes in the pattern of aortic dimensions leading to a shift from one aortic phenotype to another during the follow-up. As secondary endpoints, the rates of surgical operation on the aorta and/or valve and of aortic complications (e.g., rupture, dissection) were assessed by telephone interview and hospital chart review (98.5% completeness of data).

Statistical analysis. Continuous variables were tested for normality of distribution and accordingly summarized as mean ± SD or median (interquartile range [IQR]) and compared between 2 or more groups through unpaired Student *t* test and analysis of variance or Mann-Whitney *U* test and Kruskal-Wallis *H* test, respectively. The growth rate variable had asymmetric distribution; however, it is presented both as median (IQR) and as mean ± SD to allow comparison with reports in the literature. Categorical variables are presented as n (%) and were compared by chi-square test with the Fisher method. Multivariable binary logistic regression models were developed with the forward stepwise method to predict: 1) a growth >0 at the ascending and root level separately; and 2) a fast growth (fifth quintile) at the same levels, both in the overall cohort and in the RL and RN groups. The valve morphotype, the aorta phenotype, and all of the other baseline variables listed in Table 1 were tested for univariate association with the above dependent variables, and those showing significant association were entered as covariates in logistic models, with the follow-up time variable (as natural logarithm) always included as well. Analysis was performed through SPSS statistical software version 16.0 (SPSS, Chicago, Illinois); significance level was set at $p < 0.05$.

RESULTS

Valve morphotypes and aortic phenotypes at baseline. Ninety-two patients had RL valve morphotype (69%) and 41 had RN morphotype (31%). Aortic diameters at presentation are reported in Table 1. A no-dilation phenotype was present in 39 patients (29.3%), an ascending phenotype in 76 (57.1%), and a root phenotype in 18 (13.5%). Comparisons between valve morphotypes and among aortic phenotypes in terms of baseline parameters are reported in Tables 1 and 2, respectively. A significant association of RN type with aortic valve stenosis, female sex, MVP, and smaller dimensions of the aortic root was observed. The root phenotype was consistently associated with RL-BAV and male sex.

Follow-up data. Mean follow-up time was 4.0 ± 2.7 years (median 3 years; IQR: 1.8 to 5.2 years), ranging from 1 to 12 years (cumulative 535 patient-years). Aortic diameters at last follow-up echocardiography were 3.7 ± 0.6, 3.5 ± 0.6, and 4.2 ± 0.7 cm at sinuses, STJ, and ascending level, respectively. Fifty-three patients (40%: 40 with ascending phenotype, 10 with no-dilation phenotype, and 3 with root phenotype) underwent surgery, including isolated aortic valve replacement (19%) or aorta replacement with or without valve operation (21%). All other patients are still under continuing surveillance. Aortic dissection/rupture did not occur in this series. The mean growth rate was 0.3 mm/year at the root (median 0 mm/year; IQR: 0.0 to 0.4 mm/year) and 0.6 mm/year at the ascending level (median 0.3 mm/year; IQR: 0.0 to 0.8 mm/year). The STJ growth rate was judged to be insignificant (mean 0.09 mm/year; median

Table 1. Main Baseline Characteristics in the Overall Population and in the 2 Subgroups of Valve Morphotype

	All Patients	RL Morphotype (n = 92)	RN Morphotype (n = 41)	p Value*
Age, yrs	46 ± 15	46 ± 15	47 ± 15	0.71
Female	35 (26)	19 (21)	16 (39)	*0.02*
BSA, m^2	1.85 ± 0.2	1.86 ± 0.2	1.81 ± 0.2	0.13
Valve function				*<0.0001*
Normal	66 (50)	54 (59)	12 (29)	
Stenosis (≥moderate)	32 (24)	13 (14)	19 (46)	
Regurgitation (≥moderate)	35 (26)	25 (27)	10 (24)	
BAV stenosis (any degree)	60 (45)	33 (36)	27 (66)	*0.002*
BAV regurgitation (any degree)	90 (68)	64 (70)	26 (63)	0.55
Ejection fraction, %	60 ± 5	61 ± 5	59 ± 6	0.11
LVEDd, cm	5.3 ± 0.6	5.3 ± 0.6	5.2 ± 0.6	0.19
LVSV, ml	92 ± 23	94 ± 21	87 ± 26	0.12
IVSTd, cm	1.09 ± 0.2	1.08 ± 0.2	1.10 ± 0.2	0.50
COPD	6 (4.5)	4 (4)	2 (5)	0.60
Hypertension	18 (13)	13 (14)	5 (12)	0.50
Chronic obstructive arteriopathy	10 (7)	5 (5)	5 (12)	0.16
Mitral valve prolapse/billowing	28 (21)	14 (15)	14 (34)	*0.014*
AR + MVP association	11 (8)	6 (6)	5 (12)	0.22
Aortic root diameter, cm	3.6 ± 0.6	3.8 ± 0.5	3.2 ± 0.3	*<0.0001*
STJ diameter, cm	3.4 ± 0.5	3.6 ± 0.5	3.0 ± 0.4	*<0.0001*
Ascending diameter, cm	4.1 ± 0.7	4.2 ± 0.7	3.9 ± 0.7	*0.029*
Root relative size, cm/m^2	1.9 ± 0.3	2.1 ± 0.3	1.8 ± 0.2	*<0.0001*
Ascending relative size, cm/m^2	2.2 ± 0.4	2.3 ± 0.5	2.2 ± 0.4	0.22
Small aortic root	16 (12)	3 (3)	13 (32)	*<0.0001*

Values are mean ± SD or n (%). *RL versus RN (unpaired Student *t* or chi-square test). Italicized p values are statistically significant.
AR + MVP = moderate or worse aortic regurgitation plus mitral valve prolapse; BAV = bicuspid aortic valve; BSA = body surface area; COPD = chronic obstructive pulmonary disease; IVSTd = interventricular end-diastolic septum thickness; LVEDd = left ventricular end-diastolic diameter; LVSV = left ventricular stroke volume; RL = right-left coronary; RN = right-noncoronary; STJ = sinotubular junction.

0 mm/year; IQR: 0.0 to 0.3 mm/year); therefore, no analysis of predictors was performed for this level.

The aortic root diameter increased over time in 41% of patients, and the ascending diameter increased in 55%. In 32% of patients, no growth was observed at any level. Comparisons between BAV morphotypes and among aorta phenotypes in terms of follow-up data are depicted in Table 3; during comparable follow-up times, patients with root phenotype showed significantly higher incidence of fast progression of the ascending diameter.

Predictors of aortic diameter progression in the follow-up. In univariate analysis, length of follow-up (p = 0.012), absence of aortic stenosis (p = 0.021), AR + MVP (p = 0.031), and AR (any degree; p = 0.038) were significantly associated with a progression of the aortic root diameter. The logistic regression model, adjusted for the follow-up time, identified the AR + MVP association (odds ratio [OR]: 7.5; 95% confidence interval [CI]: 1.8 to 49.0; p = 0.014) as an independent predictor of root diameter increase, whereas the presence of any degree of aortic stenosis was a protective factor (OR: 0.2; 95% CI: 0.08 to 0.6; p = 0.004). In univariate analysis, AR + MVP (p = 0.030), presence of AR (any degree; p = 0.037), follow-up time (p = 0.04), and COPD (p = 0.05) were associated with increasing ascending diameter over time. AR (any degree; OR: 2.3; 95% CI: 1.0 to 5.1; p = 0.03) was the only independent predictor.

Predictors of fast progression of aortic diameter. A fast-progressing aortic diameter was defined as a growth rate falling within the top quintile of growth rates distribution: >0.9 mm/year for the ascending level and >0.5 mm/year for the root level. A fast progression of the root diameter was associated with RN valve morphotype (p = 0.001) (Table 3), smaller aortic root at baseline (3.3 ± 0.5 vs.

Table 2. Baseline Characteristics in the 3 Subgroups of Aortic Phenotype

	No-Dilation Phenotype (n = 39)	Ascending Dilation Phenotype (n = 76)	Root Dilation Phenotype (n = 18)	p Value*
Age, yrs	39 ± 17	52 ± 12	39 ± 11	*<0.001*
Female	10 (26)	25 (33)	0	*0.007*
BSA, m^2	1.85 ± 0.2	1.83 ± 0.2	1.93 ± 0.2	0.13
RN morphotype	17 (44)	24 (32)	0	*0.001*
Valve function				0.17
Normal	16 (41)	40 (53)	10 (56)	
Stenosis (≥moderate)	13 (33)	18 (24)	1 (6)	
Regurgitation (≥moderate)	10 (26)	18 (24)	7 (39)	
BAV stenosis (any degree)	17 (44)	41 (54)	2 (11)	*0.003*
BAV regurgitation (any degree)	28 (72)	47 (62)	15 (83)	0.17
Ejection fraction, %	61 ± 4	60 ± 6	60 ± 8	0.42
LVEDd, cm	5.2 ± 0.5	5.2 ± 0.6	5.7 ± 0.5	*0.011*
LVSV, ml	87 ± 24	90 ± 22	109 ± 15	*0.002*
IVSTd, cm	1.1 ± 0.2	1.1 ± 0.2	1.0 ± 0.1	0.36
COPD	0	5 (7)	1 (6)	0.26
Hypertension	1 (2.6)	14 (18)	2 (11)	*0.045*
Chronic obstructive arteriopathy	4 (10)	6 (8)	0	0.52
Mitral valve prolapse/billowing	12 (31)	16 (21)	0	*0.016*
AR + MVP association	4 (10)	7 (9)	0	0.49
Aortic root diameter, cm	3.2 ± 0.3	3.7 ± 0.5	4.2 ± 0.4	*<0.0001*
STJ diameter, cm	2.9 ± 0.4	3.5 ± 0.5	3.6 ± 0.4	*<0.0001*
Ascending diameter, cm	3.2 ± 0.3	4.6 ± 0.5	3.8 ± 0.5	*<0.0001*
Root relative size, cm/m^2	1.7 ± 0.2	2.0 ± 0.3	2.2 ± 0.2	*<0.0001*
Ascending relative size, cm/m^2	1.7 ± 0.2	2.5 ± 0.3	2.0 ± 0.2	*<0.0001*

Values are mean ± SD or n (%). *Comparison among phenotypes was by analysis of variance or chi-square test. Italicized p values are statistically significant. Abbreviations as in Table 1.

3.7 ± 0.6 cm; p = 0.009), and greater left ventricular end-diastolic diameter (5.5 ± 0.6 cm vs. 5.2 ± 0.6 cm; p = 0.016). The RN fusion pattern was a significant independent predictor in logistic regression (Table 4); however, in RN patients, the mean root diameter at the end of the follow-up was within the normal range (3.3 ± 0.3 cm). Significant univariate correlates of fast increasing ascending diameter were root phenotype (50% vs. 17% in all the other patients; p = 0.006), COPD (p = 0.023), and AR (any degree; p = 0.028). In multivariate analysis, only root phenotype emerged as an independent predictor of fast ascending growth (Table 4). The predictors of fast aortic growth in the 2 valve morphotype subgroups are presented in Table 4.

Phenotypic evolution. The most common phenotypic combination (i.e., the RL/ascending phenotype) relatively rarely showed fast progression: 6% for the root level and 10% for the ascending level. Phenotype changes during the follow-up are illustrated in Figure 1.

DISCUSSION

Most studies on the natural or clinical history of BAV aortopathy have focused on the risk of aortic events, including aortic dissection or rupture, sudden death, and surgery for aortic aneurysm (4,5). Conversely, few small studies, mainly in pediatric populations (18,20), have looked at aortic growth rates. After the evidence that dissection can also occur at small aortic diameters, the threshold dimension mandating surgical treatment has been progressively lowered in official guidelines, whereas the yearly growth prompting surgery has long remained unchanged (>0.5 cm/year), without distinction among different etiologies (21). Only recently, earlier surgery has been recommended for patients with aortic diameter increase >2 mm/year

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Table 3. Follow-Up Data

	Valve Morphotype			Aorta Phenotype			
	RL (n = 92)	RN (n = 41)	p Value RL vs. RN	No Dilation (n = 39)	Ascending Dilation (n = 76)	Root Dilation (n = 18)	p Value Among Phenotypes
Follow-up, yrs	3.3 (2.0–5.3)	2.4 (1.4–4.8)	0.08	3 (1.8–5.4)	3.2 (2–5)	2.2 (1.7–5.2)	0.75
Growth rate: root, mm/year	0 (0–0.31)	0 (0–1.2)	*0.05*	0 (0–0.4)	0 (0–0.4)	0 (0–0.3)	0.27
Growth rate: STJ, mm/year	0 (0–0.19)	0 (0–0.28)	0.34	0 (0–0.1)	0 (0–0.5)	0 (0–0)	0.79
Growth rate: ascending, mm/year	0.2 (0–0.68)	0.35 (0–1.3)	0.07	0.2 (0–0.6)	0.3 (0–0.7)	0.6 (0–1.3)	0.43
Progression of root diameter	37 (40)	18 (44)	0.42	16 (41)	34 (45)	5 (28)	0.45
Progression of ascending diameter	49 (53)	24 (58)	0.35	20 (51)	43 (57)	10 (56)	0.91
Fast progression of root diameter	10 (11)	15 (37)	*0.001*	8 (20)	14 (18)	3 (17)	0.95
Fast progression of ascending diameter	17 (18)	12 (29)	0.12	9 (24)	11 (14)	9 (50)	*0.02*
Increase in aortic stenosis degree	16 (17)	9 (22)	0.35	5 (13)	19 (25)	1 (6)	0.11
Increase in aortic regurgitation degree	16 (17)	6 (15)	0.45	5 (13)	14 (18)	3 (17)	0.80

Values are median (interquartile range) or n (%). Mann-Whitney and Kruskal-Wallis tests were used to compare follow-up times and growth rates; chi-square test (with Fisher exact correction) was used to compare the percentages of progressing cases and fast progressing cases. Italicized p values are statistically significant. Abbreviations as in Table 1.

(22). In the present series, mean growth rates fell within the range of previously reported values (23,24); only 7 patients (5.3%) showed an increase >2 mm/year. Thus, even this cutoff might be too high. Although typically progressive in its nature (diameters remained stable over time in only 32% of patients), BAV aortopathy was generally an indolent disease, with slow mean growth rates. Nevertheless, the mean ascending diameter increase in our fast progression group was 2 mm/year; therefore, our definition successfully identified patients at higher risk of requiring surgery (22).

Methods for accurate prognostic stratification of BAV aortopathy are not available today (2). Factors correlated with a faster growth of the aorta could be considered among the possible markers of more severe aortopathy. Thanassoulis et al. (23) identified RL pattern as a predictor of fast progression (>1.01 mm/year) of the ascending tubular tract diameter in 147 patients with BAV followed for 3.8 $\pm$ 1.4 years, whereas Holmes et al. (18), in 112 pediatric patients, observed significantly greater z-score increase with RN fusion. Such contrasting results may depend on the dissimilar ages of the cohorts and different statistical methods employed (logistic vs. linear regression) (18,23). The present series, although not larger than previous ones, was the first to distinguish not

Table 4. Multivariate Predictors of Fast Growth of the Aortic Diameter

	Predictor	OR	95% CI	p Value
Dependent variable: ascending tract growth rate >0.9 mm/year				
All patients	Root phenotype	14.0	3.2–62	*0.001*
RL type	Root phenotype	7.0	2.0–24	*0.002*
RN type	Aortic regurgitation (any degree)	20.0	1.3–76	*0.03*
Dependent variable: root growth rate >0.5 mm/year				
All patients	RN type	3.7	1.1–12	*0.03*
RL type	Small aortic root*	28.0	2.2–39	*0.011*
RN type	Fast progression of the ascending diameter	6.2	1.0–37	*0.04*

For each segment of the aorta (ascending and root), 3 separate logistic regression models were developed: 1 for the entire cohort and 1 for each of the 2 subgroups of BAV morphotype. In each model, among all the study variables (listed in Table 1), only those showing significant univariate association with the outcome variable (see Results) were entered as covariates. Italicized p values are statistically significant. *Small aortic root = diameter at the sinuses >2 SD smaller than the mean expected normal value (see Methods), irrespective of the diameter at the ascending tract (a feature possibly associated with either the normal or ascending phenotypes).
CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

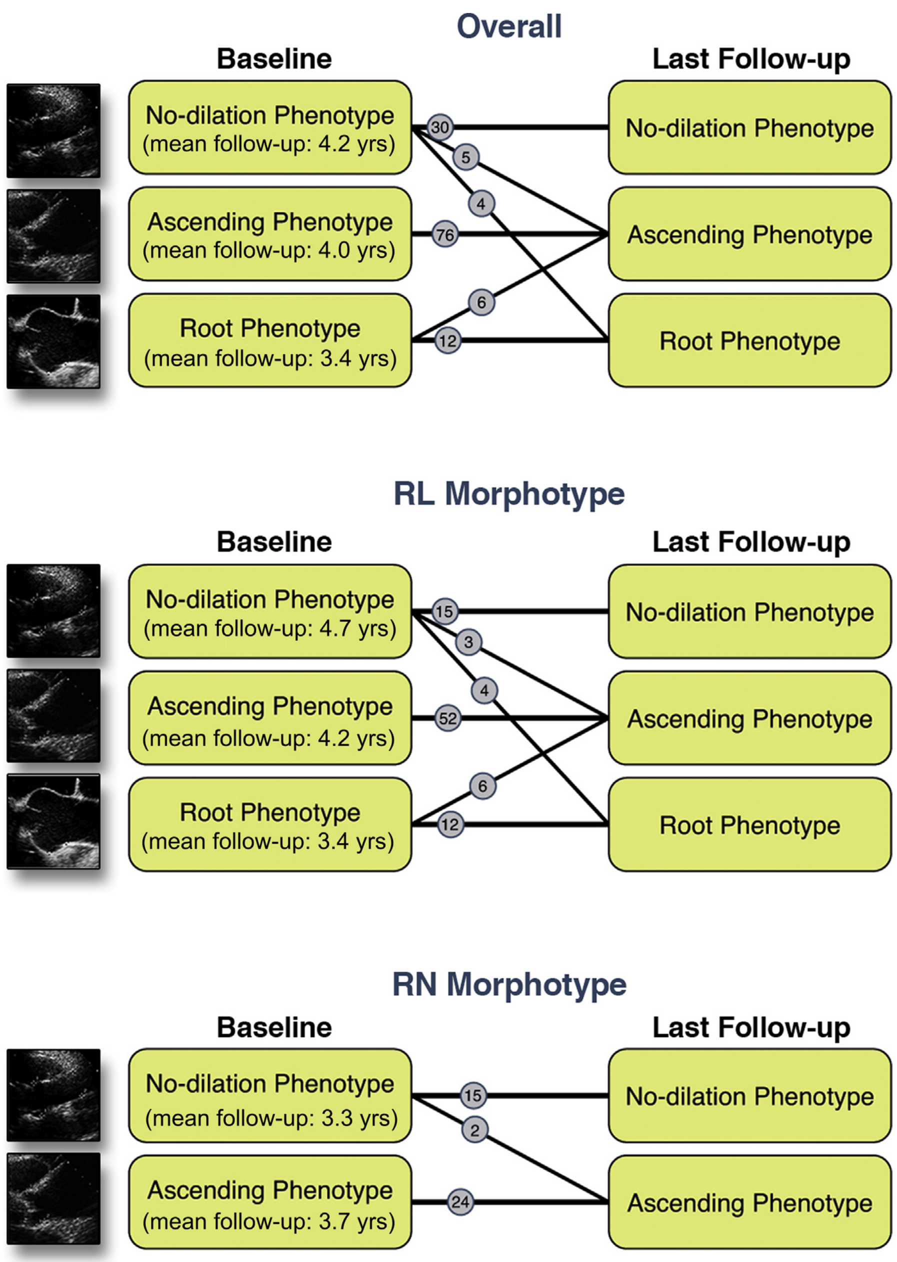

Figure 1. Changes in Aortic Configuration Over Time

Cases of shifting from one type of dilation to another were observed exclusively among patients with root phenotype (i.e., the ascending diameter eventually overcame the already enlarged sinus diameter). Although length of follow-up was not standardized due to the retrospective design, the follow-up times were not significantly different among phenotype groups (Table 3). RL = right-left coronary; RN = right-noncoronary.

only valve morphotypes but also aortic phenotypes; notably, the 2 aortic tracts (root and tubular ascending) had distinct determinants of both growth and fast growth (Table 4).

The coexistence of BAV regurgitation and MVP, an association previously pointed out by others (19), independently predicted a growth of the aortic root over time. This may support the previous suggestion that AR + MVP be subtended by a congenital weakness affecting the whole anatomic continuity spanning from the anterior mitral leaflet to the ascending aorta (25). However,

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a biomechanical explanation for the finding cannot be excluded (26). Aortic valve stenosis at baseline was conversely a predictor of stability of the root diameter during follow-up, consistent with our previous cross-sectional study on 280 patients with BAV (8).

Increase of the ascending diameter over time was predicted by AR, concurring with the results forwarded by Roberts et al. (27), whereby loss of medial elastic fibers was more frequent in the BAV aorta with pure AR than with stenosis. Our previous studies had already suggested that the aortopathies associated with BAV stenosis and regurgitation may be subtended by disparate pathobiology mechanisms (28). However, those pathology studies did not discriminate between root and ascending phenotypes (27,28). Patients with AR BAV should probably be regarded as more prone to dilation progression, and eventually, provided an adequately long follow-up time, to aneurysm development.

Greater absolute dimensions of the vessel did not predict fast growth of the aorta, consistent with previous studies (18,20,23). In contrast, in the RL-BAV patient subgroup, root diameter smaller than expected based on age and BSA was an independent predictor of rapid growth at the sinus level (>0.5 mm/year). Consistently, in the overall study population, rapid sinus growth was predicted by RN fusion, a valve morphotype showing significantly smaller root dimensions (Table 1) like in other series (9,20). Importantly, the mean root dimension in patients with RN-BAV was still in the normal range at last follow-up, and no patient with RN-BAV developed a root phenotype (Fig. 1). Therefore, RN fusion might not imply an increased risk per se; our data might have merely depicted an inverse relation between root diameter and growth rate, consistent with the already reported evidence that larger diameter is associated with greater stiffness, which, in turn, is correlated with lower rates of diameter increase (29). Concordantly, in a recent study by Fernandes et al. (20), the annual change in aortic root z-score was significantly greater in patients with BAV with a baseline z-score ≤2 than in those with a z-score >2.

For the ascending aortic diameter, the only significant independent predictor of fast growth was the root phenotype; at least a proportion of patients with root phenotype tended to develop diffuse dilation of the entire ascending aorta. This finding supports the previously forwarded hypothesis (8,12) that the root phenotype identifies those patients in whom the expression of some congenital aortic wall defect overtakes the pathogenetic role of the hemodynamic abnormalities inherent to valve malformation. We observed the root phenotype mainly in male patients, generally with nonstenotic RL-BAV, younger age, and larger BSA than patients with ascending phenotype. Biner et al. (13) reported increased aortic diameters and impaired aortic wall load-bearing properties in first-degree relatives of a BAV cohort featuring an unusually high rate of root phenotype (43%). In a small observational surgical study (12), freedom from adverse aortic events following isolated aortic valve replacement was significantly lower in patients with root phenotype. Assessment of the reason for rapid dilation of the ascending tract in patients with root phenotype is beyond the scope of this study; however, the present findings underscore the importance of distinguishing the 2 types of aortic dilation in future basic research studies on BAV aortopathy mechanisms.

In patients with RN-BAV morphotype, never associated with a root phenotype in this series, AR independently predicted fast growth of the ascending diameter. Notably, AR is typically associated with the root phenotype (8,12); therefore, it could represent a surrogate marker of intrinsic aortic wall fragility in patients with RN-BAV. We could speculate that a gene defect possibly underlying the "malignant" form of BAV aortopathy could be a quantitative trait, with expression that could be modified by interaction with valve morphotype, yielding AR and root phenotype in patients with RL-BAV and AR alone in patients with RN-BAV.

Study limitations. Due to the relatively small numbers, this study remains exploratory in nature, and conclusions need further verification. The lack of a left-noncoronary morphotype group must be acknowledged. This fusion pattern is extremely rare (2% in this cohort); without a considerably larger sample, any significant association with the progression of aortopathy could not be ruled out. Our diameters may not be comparable with others' measurements by the leading-edge to leading-edge method; however, growth rates (and therefore our main results) were not affected by this limitation. Another limitation is inherent to the echocardiographic method: a measurement at the distal ascending aorta (just proximal to the brachiocephalic trunk) was available only in 90% of patients and at the arch only in 61%. Due to the incompleteness of data, these diameters were not included in the analysis; however, dilation extending beyond the mid-ascending aorta was rare (12 of 120 patients). Finally, the present study is affected by the intrinsic referral bias that limits every study based on outpatient data. Few community-based studies have been performed on patients with BAV (4), none of which searched for aortic growth predictors.

CONCLUSIONS

Within the heterogeneity of manifestations of BAV aortopathy, the present study identified phenotype markers predicting the progression of the aortic diameter. Translated into clinical practice, our findings might help stratify patients to personalize both surveillance and surgical indications. In particular, the aortopathy form with predominant dilation at the sinus level, namely the root phenotype, may represent a higher-risk condition, which deserves closer follow-up and earlier intervention.

Reprint requests and correspondence: Dr. Alessandro Della Corte, Department of Cardiothoracic Sciences–Second University of Naples, Cardiovascular Surgery and Transplant–V. Monaldi Hospital, via L Bianchi, 80131 Naples, Italy. *E-mail:* aledellacorte@libero.it.

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